Discovery of consensus gene signature and intermodular connectivity defining self-renewal of human embryonic stem cells.

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Public Summary:
Our understanding of self-renewal and differentiation capacity of human embryonic stem cells (hESCs) remains elusive on the detailed molecular mechanisms. Our current study elucidates the global regulation of stem cell beyond the well-known stem cell factors by combining over 33 microarrays and the latest bioinformatic tools. We examined if there are a set of key genes consistently altered during differentiation of hESCs regardless of differentiation conditions. By comprehensive genome-wide consensus microarray analyses, we have profiled gene expression signatures that are most significantly affected by differentiation in hESCs from our own microarray data sets as well as publically available microarrays. Our finding has unveiled the novel molecular markers that determine self-renewal and form intramodular hubs. Bioinformatics approach for the identification of new molecular markers defining undifferentiated hESCs, interacting partners and interconnectivity analyses may contribute to delineating molecular mechanisms of stem cell self-renewal/differentiation and can be a useful tool to identify molecular factors inducing stemness from different cell types.

Scientific Abstract:
Molecular markers defining self-renewing pluripotent embryonic stem cells (ESCs) have been identified by relative comparisons between undifferentiated and differentiated cells. Most of analysis has been done under a specific differentiation condition that may present significantly different molecular changes over others. Therefore, it is currently unclear if there are true consensus markers defining undifferentiated hESCs. To identify a set of key genes consistently altered during differentiation of hESCs regardless of differentiation conditions we have performed microarray analysis on undifferentiated hESCs (H1 and H9) and differentiated EB's and validated our results using publicly available expression array data sets. We constructed consensus modules by Weighted Gene Correlation Analysis (WGCNA) and discovered novel markers that are consistently present in undifferentiated hESCs under various differentiation conditions. We have validated top markers (downregulated: LCK, KLKB1 and SLC7A3; upregulated: RhoJ, Zeb2 and Adam12) upon differentiation. Functional validation analysis of LCK in self-renewal of hESCs by using LCK inhibitor or gene silencing with siLCK resulted in a loss of undifferentiation characteristics- morphological change, reduced alkaline phosphatase activity and pluripotency gene expression, demonstrating a potential functional role of LCK in self-renewal of hESCs. We have designated hESC markers to interactive networks in the genome, identifying possible interacting partners and showing how new markers relate to each other. Furthermore, comparison of these data sets with available datasets from iPSCs revealed that the level of these newly identified markers were correlated to the establishment of iPSCs, which may imply a potential role of these markers in gaining of cellular potency. Stem Cells 2014.